AMENDED SPECIFICATION

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PATENT SPECIFICATION

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International Classification:—C 07 c, d

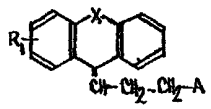
COMPLETE SPECIFICATION

New Dibenzo-Oxepin and -Thiepin Derivatives

We, C. F. BOEHRINGER & SOEHNE G.M.B.H., a body corporate organised under the laws of Germany, of Mannheim-Waldhof, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new dibenzo-oxepin and thiepin derivatives and with the preparation thereof.

The new compounds according to the present invention are basic dibenzo - (b,e) - oxepin or dibenzo - (b,e) - thiepin derivatives of the general formula:—



(I)

in which X is an oxygen or sulphur atom, R_1 is a hydrogen or halogen atom or an alkyl or alkoxy radical and A is a tertiary amino group with the proviso that where X is a Sulphur atom and R_1 is a hydrogen atom, A is other than a dimethylamino group; and the acid addition salts and quaternary ammonium compounds thereof.

We have found that these compounds can be produced in a simple and smooth manner and in very good yields when dibenzo - (b,e) - oxepin - 11 - ones or dibenzo - (b,e) - thiepin - 11 - ones of general formula (II) are reacted with Grignard compounds of the general formula

$$Hal—Mg—CH_2—CH_2—CH_2—A$$

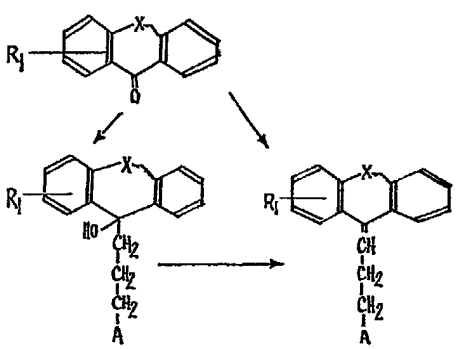
and water split off from the reaction product.

The Grignard reaction of the dibenzo - (b,e) - oxepin- or thiepin - 11 - ones (II) takes place in known manner; the corresponding Grignard compound is first produced from magnesium and an aminoalkyl halide in a suitable solvent, preferably tetrahydrofuran, a solution of the dibenzo - (b,e) - oxepin- or thiepin - 11 - one allowed to drop in at about 20°—30°C. and the reaction mixture subsequently heated for 3 hours at about 40—50°C. By decomposition of the reaction product with an ammonium chloride solution and extraction with ether, there are obtained, after the usual working up, compounds of general formula (III). The carbinols (III) are now converted in known manner, for example by treatment with alcoholic hydrochloric acid, into the dibenzo - (b,e) - alkylidene - oxepins or -thiepins (I).

For the production of the new compounds I, the isolation of the intermediate products III is, however, not absolutely necessary.

On the contrary, the Grignard reaction and the splitting off of water can very advantageously be carried out as a "one pot process". Thus, if the decomposition of the Grignard adduct is carried out by means of hydrochloric acid with subsequent boiling, then the desired alkylidene compounds I are obtained in a direct way.

(II)

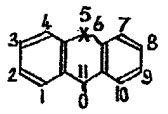


(III) (I)

The preferred tertiary amino groups A are, for example, dialkylamino groups or nitrogen-containing heterocyclic radicals, such as piperidino, pyrrolidino, morpholino and piperazino radicals, which can possibly also be substituted (e.g. the radicals of N-alkyl, N-aryl-, N-aralkyl- or N-hydroxyalkyl-piperazines, piperidones, piperidoles, alkoxy- or alkyl-piperidines or those piperidines which bear in the 2,6-position a di- or trimethylene bridge, such as N-nortropanes, N-norgranatanes, N-nortropanones, N-norgranatanones, N-mortropanols or N-norgranatanols).

The new compounds of the present invention possess interesting pharmacological properties and, on account of their psychotropic effect, especially their tranquilising action, are indicated for use in psychiatric pharmacotherapy.

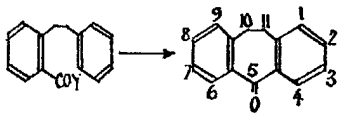
The dibenzo-(b,e)-oxepins and -thiepins used as starting materials are themselves new compounds of the general formula:—



(IV)

wherein X is an oxygen or sulphur atom.

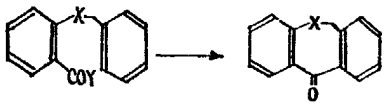
In the literature there has hitherto only been described 10,11-dihydro-dibenzo-(a,d)-cyclohepten-5-one of the formula (V) (in which the X of the above general formula IV is thus $=CH_2$). This compound can be obtained by the condensation of dibenzyl-o-carboxylic acid with polyphosphoric acid (Protiva et al., Coll.Czech. chem. Comm., *24*, 3955/1959 or Campbell et al., Helv., *36*, 1489/1953) or from dibenzyl-o-carboxylic acid chloride with aluminium chloride in carbon disulphide (Treibs et al., Ber., *83*, 367/1950; Ber., *84*, 671/1951; Cope et al., J.A.C.S., *73*, 1673/1951, Bergmann et al., Bull Soc. chem. France, 1951, 684). The reaction is illustrated by the following equation:—



(V)

wherein Y is a chloride atom or a hydroxyl radical.

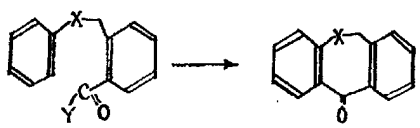
If, now, an attempt is made to prepare the compounds of general formula (IV) i.e. dibenzo-(b,e)-oxepin- or -thiepin-11-one, in an analogous manner by the condensation of benzyl salicylic or benzyl thiosalicylic acid or their acid halides, then there is either no reaction or decomposition products are formed. In other words, a reaction according to the equation:—



(IV)

wherein X is an oxygen or sulphur atom and Y is a halogen atom or a hydroxyl radical, does not take place.

We have now found that it is, surprisingly, possible to prepare these compounds of general formula (IV) in a smooth and simple manner with outstanding yields when, instead of the benzyl salicylic or benzyl thiosalicylic acid or its acid halides, the corresponding isomeric compounds, i.e. the *o*-(phenoxy-methyl) or *o*-(phenylmercaptomethyl)-benzoic acids or their acid halides are internally condensed, as illustrated in the equation:—



(VI) (IV)

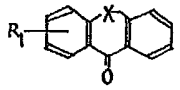
wherein X and Y have the same meaning as above.

According to the above-described negative findings in the case of the attempted condensation of benzoyl salicylic or benzyl thiosalicylic acids or their acid halides, it was completely unexpected that the process with the isomeric acids could be carried out at all.

The ring closure reaction of compounds of general formula (VI) in which Y is a hydroxyl group can be carried out with various dehydrating agents. A preferred process is the splitting off of water by means of phosphoric acid esters or polyphosphoric acid.

The splitting off of hydrogen halide from compounds of general formula (VI) in which Y is a halogen atom can be achieved with various hydrogen halide-splitting agents, such as aluminium chloride. This reaction can, however, also be successfully carried out, with outstanding yields, by simple heating of the acid halides (VI) with or without the use of solvents. The preparation of the acid halides by halogenation of the corresponding acids (VI) can be combined with the splitting off of hydrogen halide, thus providing an advantageous "one pot process".

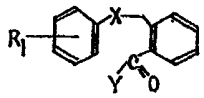
We have also found that, according to this process, it is possible to prepare substituted dibenzo-oxepines and -thiepins of the general formula:—



(II)

wherein R_1 and X have the same meaning as above.

The process is characterized in that correspondingly substituted *o*-(phenoxymethyl)-benzoic acids or *o*-(phenylmercaptomethyl)-benzoic acids or their acid halides of the general formula:—



(VII)

in which X, Y and R_1 have the same meaning as above, are internally condensed in the manner described above.

The following Examples 1 to 11 illustrate the preparation of the new starting compounds and Examples 12 and 13 illustrate the new products of the present invention:—

EXAMPLE 1.

Dibenzo-(b,e)-oxepin-11-one

a) *Dehydration of o-(phenoxymethyl)-benzoic acid.*

129 g. phosphorus pentoxide are added portionwise, with stirring, to 85 ml. absolute ethanol, initially at room temperature and subsequently, with cooling, at about 50—80°C. At the end of the addition, the flask content is heated for about one hour at 95—100°C. until all the phosphorus pentoxide has dissolved. 68.4 g. *o*-(phenoxymethyl)-benzoic acid is now added, with stirring, in two portions at 90°C. After the addition of the first half, the reaction mixture is heated at 100°C. for 15 minutes and, after the addition of the remaining amount, is heated at 100°C. for 30 minutes. The reaction product is, while still hot, poured on to ice and extracted with ether. The ethereal extracts are first washed with 2% sodium bicarbonate solution, then with 5% sodium hydroxide solution and subsequently with water, until neutral. After drying with anhydrous sodium sulphate, the ether extract is treated with animal charcoal at room temperature, filtered and the solvent evaporated off. The ether residue yields, upon distillation in a high vacuum, 53.8 g. dibenzo-(b,e)-oxepin-11-one of b.p. 142—145°C/0.2 mm Hg, i.e. 85.5% of theory. The distillate solidifies in the receiver and has a melting point of 67—70°C; by recrystallision from ligroin, the melting point increases to 71—72°C. A further recrystallisation from ethanol does not result in any increase in the melting point.

The *o*-(phenoxymethyl)-benzoic acid required as starting material is described in the literature (British Patent No. 773,594; F. G. Mann and H. C. Stewart, Soc., *1954*, 2819; A. Oppe, Ber., *46*, 1096/1913). However, for the preparation, it is expedient to choose a simpler and more productive method:

367.5 g. ω-bromo-*o*-tolyl bromide (prepared according to W. Davies and W. H. Perkin jr., J. chem. Soc., *121*, 2203/1922) are dissolved, with cooling at about 10°C., in 660 ml. absolute ethanol. An alcoholic sodium phenolate solution (prepared from 62 g. sodium, 1320 ml. ethanol and 250 g. phenol) is allowed to drop in, with stirring, at room temperature and the flask content subsequently heated, with stirring, to boiling for 2 hours. After cooling, the precipitate formed is filtered off with suction, the greater part of the ethanol evaporated in a vacuum on a water bath and the residue mixed with water and ether. The ethereal portions are washed neutral with dilute so-

dium hydroxide solution and then with water and dried. The ether residue remaining behind after the removal of the solvent is heated to boiling for 2 hours in a solution of 130 g. potassium hydroxide in 1200 ml. methanol. The solvent is evaporated in a vacuum and the residue taken up in water and ether. The separated and filtered aqueous portions are mixed, with cooling, with dilute hydrochloric acid until a strongly acidic reaction is obtained. The precipitate formed is collected in a suction filter funnel, well washed with water and dried in a vacuum at about 50°C. Yield: 208 g. *o*-(phenxoymethyl)-benzoic acid of m.p. 125—126°C., i.e. 69% of theory, referred to the ω-bromo-*o*-tolyl bromide.

b) *Splitting off of hydrogen halide from o-(phenoxymethyl) benzoyl chloride.*

I) 5 g. *o*-(phenoxymethyl) benzoyl chloride are heated in a stream of nitrogen for 2½ hours in an oil bath at 100—110°C. and then for ½ hour at 150—160°C. The subsequently high vacuum distillation yields 2.6 g. (61% of theory) dibenzo-(b,e)-oxepin-11-one (b.p. 150—160°C/0.3 mm Hg; m.p. 60—64°C.) By recrystallisation from ligroin, the melting point increases to 67—70°C.

II) 5 g. *o*-(phenoxymethyl)-benzoyl chloride and 5 ml. xylene are heated to boiling for 5 hours. After removal of the solvent in a vacuum, the evaporation residue is distilled in a high vacuum. Yield: 3.4 g. (81% of theory) dibenzo-(b,e)-oxepin-11-one. (b.p. 144—150°C/0.3 mm Hg.; m.p. 68—71°C).

III) 11.4 g. *o*-(phenoxymethyl)-benzoic acid and 4.5 ml. thionyl chloride are heated to boiling for 8 hours in 12 ml. xylene. The residue remaining behind after evaporation of the solvent yields 7.7 g. (73% of theory) dibenzo-(b,e)-oxepin-11-one. (b.p. 142—152°C/0.3 mm Hg; m.p. 64—68°C).

Better yields and a purer product are obtained when working without solvent:

5.7 g. (0.025 mol) *o*-(phenoxymethyl)-benzoic acid and 6 ml. thionyl chloride are heated to boiling for 2 hours. The excess thionyl chloride is removed and the residue heated in an oil bath at 150—160°C., with the passing through of a dried current of nitrogen, until the termination of the hydrogen chloride evolution (about 2 hours). The subsequent high vacuum distillation yields 4.2 g. (80% of theory) dibenzo-(b,e)-oxepin-11-one of b.p. 142—145°C/0.2 mm Hg. (m.p. 63—66°C). After recrystallisation from isopropanol, there are obtained 3.7 g. (71% of theory) of pure product of m.p. 71—72°C.

IV) 6.7 g. aluminium chloride are added portionwise at 20—30°C. to 12.3 g. *o*-(phenoxymethyl)-benzoyl chloride in 45 ml. carbon disulphide and 10 ml. nitrobenzene, the flask content maintained for 5 hours at room temperature and subsequently heated to boiling for 1 hour. After the reaction product has been poured on to ice, the organic portions are, with the addition of ether, separated off, washed with 2% sodium bicarbonate solution, then with 5% sodium hydroxide solution and with water and the solvent removed in a vacuum. The evaporation residue yields, upon high vacuum distillation, 7.1 g. (68% of theory) dibenzo-(b,e,)-oxepin-11-one. (b.p. 143—147°C/0.2 mm Hg; m.p. 68—70°C).

The *o*-(phenoxymethyl)-benzoyl chloride used as starting material, which has not hitherto been described, can be obtained by chlorination of the corresponding acid with thionyl chloride with or without the use of a solvent.

A) 45.6 g. *o*-(phenoxymethyl)-benzoic acid and 73 ml. thionyl chloride are heated to boiling for 3 hours. After evaporation of the excess thionyl chloride in a vacuum, the residue is crystallised from ligroin. Yield: 93 g. *o*-(phenoxymethyl)-benzoyl chloride of m.p. 48—51°C, i.e. 93% of theory.

B) 7 ml. thionyl chloride in 10 ml. chloroform are added dropwise at 20—25°C. to 10.6 g. *o*-(phenoxymethyl)-benzoic acid in 25 ml. chloroform and the flask content brought to boiling for 8 hours. The filtered solution is evaporated in a vacuum and the residue recrystallised from ligroin. Yield: 9.6 g. *o*-(phenoxymethyl)-benzoyl chloride of m.p. 55—57°C, i.e. 84% of theory.

EXAMPLE 2.

Dibenzo-(b,e)-thiepin-11-one

a) 32 g. phosphorus pentoxide are added portionwise, with stirring, to 22 ml. 85% phosphoric acid, starting at room temperature and then, with periodic cooling, at 60—80°C. The flask content is heated for about 1 hour at 95—100°C. until the phosphous pentoxide is completely dissolved. 12.2 g. *o*-(phenylmercapto-methyl)-benzoic acid are now added in one amount, with intensive stirring, at 80—90°C. and the reaction mixture heated for 30 minutes at 100—110°C. The flask content, while still hot (about 80°C.) is poured on to ice and extracted with ether. The combined ethereal portions are washed several times with 5% sodium hydroxide solution, then with water, until neutral, dried with anhydrous sodium sulphate and the solvent removed (10.4 g.). The ether residue yields, after trituration with ligroin/ether, 8.2 g. (i.e. 73% of theory) dibenzo-(b,e)-thiepin-11-one (m.p. 82—86°C.). After recrystallisation from isopropanol and methanol, with the addition of animal charcoal, there are obtained 7.2 g. (64% of theory) dibenzo-(b,e) thiepin-11-one (m.p. 86—88°C.).

b) 12.2 g. *o*-(phenylmercapto-methyl)-benzoic acid are added in one amount, with intensive stirring, at about 80°C. internal temperature, to 70 g. commercial polyphosphoric acid and the mixture subsequently heated for 30 minutes at 100—110°C. The flask content, while still hot (about 80°C.). is stirred into ice water and extracted several times with ether. The combined ether extracts, after washing with 5% sodium hydroxide solution and water and drying, are freed from solvent and the evaporation residue distilled in a high vacuum. Yield: 9.2 g. dibenzo-(b,e)-thiepin-11-one of b.p. 162—165°C/0.03 mm Hg and m.p. 85—87°C, i.e. 82% of theory. By recrystallisation from isopropanol, the melting point increases to 88—89°C.

The *o*-(phenylmercapto-methyl)-benzoic acid required as starting material was obtained, analogously to *o*-(phenoxymethyl-benzoic acid, from ω-bromo-*o*-tolyl bromide and sodium thiophenolate in a yield of 80—85%; m.p. 106—109°C (c.f. British Patent No. 773,594).

EXAMPLE 3.

2-chloro-dibenzo-(b,e)-thiepin-11-one.

13.90 g. (0.05 mol) *o*-(*p*-chlorophenylmercaptomethyl)-benzoic acid are added in one amount, with stirring, at about 80°C. (internal temperature) to 70 g. commercial polyphosphoric acid and heated for 30 minutes at 130—140°C. (internal temperature). The flask content, while still hot (about 80°C.), is stirred into ice water and extracted with ether. The combined ether extracts, after washing with 5% sodium hydroxide solution and water and drying, are freed from solvent and the evaporation residue distilled in a high vacuum (11.3 g; 87% of theory; m.p. 127—130°C.). Yield: 10.5 g. 2-chloro-dibenzo-(b,e)-thiepin-11-one of b.p. 175—181°C/0.2 mm Hg and m.p. 130—132°, i.e. 81% of theory. After recrystallisation from isopropanol, the crystallisate has a melting point of 133—134°C.

The *o*-(*p*-chlorophenylmercaptomethyl)-benzoic acid required as starting material was produced as follows:

27.8 g. (0.1 mol) ω-bromo-*o*-tolyl bromide (produced according to Davies and Perkin jr., J. Chem. Soc., *121*, 2203/1922) are dissolved in 50 ml. absolute ethanol, with cooling at about 10°C. An alcoholic solution of sodium *p*-chloro-thiophenate (produced from 29 g. (0.2 mol) *p*-chlorothiophenol, 4.6 g. sodium and 100 ml. absolute ethanol) is allowed to drop in, with stirring, at room temperature and the flask content subsequently heated to boiling for 2 hours. After cooling, the precipitate obtained is filtered off and the greater part of the ethanol evaporated in a vacuum. The residue is mixed with water and ether, the ethereal portions washed with 5% sodium hydroxide solution, then with water and dried with anhydrous sodium sulphate. The ether residue (33.2 g.) remaining behind after the removal of the solvent is heated to boiling for 2 hours in a solution of 16.5 g. potassium hydroxide and 165 ml. methanol. The solvent is evaporated in a vacuum and the residue taken up in water and ether. The separated and filtered aqueous portions are mixed, with stirring, with dilute hydrochloric acid. The precipitate obtained is collected on a suction filter funnel, well washed with water and dried in a vacuum at about 50°C. If desired, the crystal mass is triturated with ligroin for the removal of coloured impurities. Yield: 22.8 g. *o*-(*p*-chlorophenylmercaptomethyl)-benzoic acid of m.p. 125—128°C, i.e. 82% of theory.

EXAMPLE 4.

2-methyl-dibenzo-(b,e)-thiepin-11-one.

25.8 g. (0.1 mol) *o*-(*p*-methyl-phenylmercaptomethyl)-benzoic acid are introduced, with stirring, at 80°C. into 140 g. polyphosphoric acid and the mixture heated for 30 minutes at 100—110°C. Working up takes place as described in more detail in Example 1. Yield: 17.3 g. 2-methyl-dibenzo-(b,e)-thiepin-11-one of b.p. 167—175°C/0.2 mm Hg and m.p. 114—118°C, i.e. 72% of theory. After recrystallisation from isopropanol, the compound melts at 119—120°C.

The *o*-(*p*-methyl-phenylmercaptomethyl)-benzoic acid used as starting product was obtained, in analogy to *o*-(*p*-chlorophenylmercaptomethyl)-benzoic acid, from ω-bromo-*o*-tolyl bromide and *p*-thiocresol in a yield of 85% of theory (m.p. 128—131°C.).

EXAMPLE 5.

2-methyl-dibenzo-(b,e)-oxepin-11-one

a) *Dehydration of* o-(p-*methyl*-*phenoxymethyl*)-*benzoic acid*

21.0 g. phosphorus pentoxide are introduced, with stirring, into 14 ml. absolute ethanol, commencing at room temperature and subsequently, with stirring, at 50—80°C. (internal temperature). At the end of the addition, the flask content was heated for about 1 hour at 95—100°C. (internal temperature) until all the phosphorus pentoxide has reacted. 12.1 g. (0.05 mol) *o*-(*p*-methyl-phenoxymethyl)-benzoic acid are added in one amount thereto at 80—90°C. and the mixture heated for 30 minutes at 100—100°C. The flask content is, while still hot (about 80°C.), stirred into ice water

and extracted with ether. The combined ether extracts, after washing with 5% sodium hydroxide solution or water and drying, are freed from solvent and the evaporation residue (10.3 g; m.p. 101—105°C.) triturated with ligroin. Yield: 8.8 g. 2 - methyl - dibenzo - (b,e) - oxepin - 11 - one of m.p. 106—108°C, i.e. 78.5% of theory. By recrystallisation from isopropanol, the melting point increases to 108—109°C.

The *o* - (*p* - methyl - phenoxymethyl) - benzoic acid used as starting material, was obtained, in analogy to *o* - (*p* - methyl - phenylmercaptomethyl) - benzoic acid, from ω - bromo - *o* - tolyl bromide and *p* - cresol in a yield of 70—75%; m.p. 118—120°C.

b) *Splitting off of hydrogen halide from* o - (p - *methyl* - *phenoxymethyl*) - *benzoyl chloride*

I) 12.1 g. (0.05 mol) *o* - (*p* - methyl - phenoxymethyl) - benzoic acid and 20 ml. thionyl chloride are heated under reflux for 1 hour. The excess thionyl chloride is removed in a vacuum, the residue (12.8 g.) taken up in 20 ml. xylene and the flask content allowed to boil for 8 hours. The crystalline slurry which precipitates out in the cold is filtered off with suction and washed with a little ligroin (4.3 g. K_1 of m.p. 106—108°C.). The xylene filtrate and the ligroin mother liquor are freed in a vacuum from solvent and the evaporation residue distilled in a high vacuum. There are obtained 5.1 g. of a distillate of b.p. 140—142°C/0.05 mm Hg, which solidifies in the receiver and shews a melting point of 91—105°C. After recrystallisation from isopropanol, the melting point is 108—109°C (4.1 g.); the mixed melting point with K_1 gives no depression. The total yield of 2 - methyl - dibenzo - (b,e) - oxepin - 11 - one is 8.4 g., i.e. 75% of theory.

II) 6.0 g. (0.025 mol) *o* - (*p* - methyl - phenoxymethyl) - benzoic acid and 6 ml. thionyl chloride are brought to boiling for 1 hour and the excess thionyl chloride removed in a vacuum on a water bath. The remaining residue is heated in an oil bath in a current of nitrogen at 130—140°C. until the end of the hydrogen chloride evolution (about 1 hour) and subsequently subjected to a high vacuum distillation. Yield: 5.3 g. 2 - methyl - dibenzo - (b,e) - oxepin - 11 - one of b.p. 147—150°C/0.1 mm Hg; i.e. 95% of theory, m.p. 103—106°C.

III) 12.1 g. (0.05 mol) *o* - (*p* - methyl - phenoxymethyl) - benzoic acid, 4 ml. thionyl chloride and 25 ml. xylene are heated to boiling for 8 hours. The reaction mixture is mixed with ether, washed with dilute sodium hydroxide solution, then with water and dried with anhydrous sodium sulphate. After removal of the solvent, the evaporation residue is distilled in a high vacuum. Yield: 9.7 g. 2 - methyl - dibenzo - (b,e) - oxepin - 11 - one of b.p. 147—150°C/0.1 mm Hg. and m.p. 96—106°C. After trituration with ligroin, 8.3 g. of the pure substance are obtained (m.p. 108—109°C.).

Example 6.

2 - methoxy - dibenzo - (b,e) - oxepin - 11 - one.

a) *Dehydration of* o - (p - *methoxy* - *phenoxymethyl*) - *benzoic acid*

The reaction of 42 g. phosphorus pentoxide with 28 ml. absolute ethanol takes place as described in Example 5 a). 25.8 g. (0.1 mol) *o* - (*p* - methoxy - phenoxymethyl) - benzoic acid are introduced at 80—90°C. and the reaction mixture heated, with stirring, for 30 minutes at 130—140°C. Working up takes place as described in more detail in Example 5 a). The ether residue (23.6 g.) Yields, upon vacuum distillation, 19.5 g. 2 - methoxy - dibenzo - (b,e) - oxepin - 11 - one of b.p. 158—162°C/0.05 mm Hg and m.p. 91—93°C, i.e. 81% of theory. By recrystallisation from isopropanol, the melting point increases to 93—94°C.

The *o* - (*p* - methoxy - phenoxymethyl) - benzoic acid used as starting material was obtained in the usual manner by the reaction of ω - bromo - *o* - toluyl bromide with *p* - methoxyphenol (yield 78% of theory, m.p. 176—178°C).

b) *Splitting off of hydrogen halide from* o - (p - *methoxy* - *phenoxymethyl*) - *benzoyl chloride.*

6.5 g. (0.025 mol) *o* - (*p* - methoxy - phenoxymethyl) - benzoic acid and 6 ml. thionyl chloride are heated to boiling for 2 hours. The excess thionyl chloride is removed in a vacuum and the residue heated in an oil bath to 200—220°C., with the passing through of nitrogen, until the end of the hydrogen chloride evolution (about 2 hours). Distillation in a high vacuum yields 4.2 g. (70% of theory) 2 - methoxy - dibenzo - (b,e) - oxepin - 11 - one of b.p. 172—175°C/0.2 mm Hg (m.p. 73—83°C). After recrystallisation from isopropanol, there are obtained 2.55 g. (42.5% of theory) of pure product (m.p. 93—94°C.).

Example 7.

2 - chloro - dibenzo - (b,e) - oxepin - 11 - one.

a) *Dehydration of* o - (p - *chlorophenoxymethyl*) - *benzoic acid*

The production takes place as described in more detail in Example 5: 13.1 g. (0.05 mol) *o* - (*p* - chlorophenoxymethyl) - benzoic acid are condensed (reaction time 30 minutes) at 130—140°C. (internal temperature) with polyphosphoric acid ester (produced from

21.0 g. phosphorus pentoxide and 14 ml. absolute ethanol). In this manner, there are obtained 11.8 g. of crude product (96.8% of theory; m.p. 65—112°C) and, after distillation, 8.7 g. 2 - chloro - dibenzo - (b,e) - oxepin - 11 - one of b.p. 162—166°C/0.5 mm Hg and m.p. 119—125°C, i.e. 71.5% of theory. After recrystallisation from isopropanol, the compound has a melting point of 126—127°C.

The *o* - (*p* - chlorophenoxymethyl) - benzoic acid used as starting material was prepared in the usual manner from ω - bromo - *o* - toluyl bromide and *p* - chlorophenol in a yield of 77% of theory (m.p. 162—164°C.).

b) *Splitting off of hydrogen halide from* o - (p - *chlorophenoxymethyl*) - *benzoyl chloride.*

13.1 g. (0.05 mol) *o* - (*p* - chlorophenoxymethyl) - benzoic acid are heated under reflux cooling for 1 hour in 20 ml. thionyl chloride, the excess thionyl chloride removed in a vacuum, the residue taken up in 20 ml. xylene and the flask content brought to the boil for 8 hours. After the addition of ether, the organic portions are washed with 5% sodium hydroxide solution, then with water, dried and freed from solvent. The evaporation residue (12.8 g.) yields upon high vacuum distillation, 9.5 g. 2 - chloro - dibenzo - (b,e) - oxepin - 11 - one of b.p. 174—176°C/0.2 mm Hg and m.p. 117—123°C, i.e. 78% of theory. After recrystallisation from isopropanol, 8.4 g. are obtained, i.e. 69% of theory (m.p. 126—127°C.).

Better yields and a purer product are obtained when working without a solvent;

6.6 g. (0.025 mol) *o* - (*p* - chlorophenoxymethyl - benzoic acid and 6 ml. thionyl chloride are heated to boiling for 2 hours. After the removal of excess thionyl chloride in a vacuum, the residue is heated on an oil bath to 130—140°C., with the passing through of nitrogen, until the end of the hydrogen chloride evolution (about 2 hours) and distilled in a high vacuum. There are thus obtained 5.3 g. (87% of theory) 2 - chloro - dibenzo - (b,e) - oxepin - 11 - one of b.p. 162—166°C/0.5 mm Hg (m.p. 120—127°C). After trituration with ligroin, the compound melts at 126—127°C.; yield: 4.2 g. (78% of theory).

Example 8.

2 - bromo - dibenzo - (b,e) - oxepin - 11 - one.

7.7 g. (0.025 mol) *o* - (*p* - bromophenoxymethyl) - benzoic acid and 6 ml. thionyl chloride are heated to boiling for 2 hours. The excess thionyl chloride is removed in a vacuum and the residue heated in an oil bath under nitrogen at 150—160°C. until the end of the hydrogen chloride evolution (about 2 hours). The flask content is distilled in a high vacuum and yields 5.8 g. (81% of theory) 2 - bromo - dibenzo - (b,e) - oxepin - 11 - one of b.p. 165—168°C/0.05 mm Hg (m.p. 126—132°C). After recrystallisation from isopropanol, there are obtained 5.2 g. (72.5% of theory) of pure product (m.p. 135—137°C.).

Example 9.

3 - methyl - dibenzo - (b,e) - oxepin - 11 - one.

As described in more detail in Example 5 a), 14 ml. absolute alcohol are allowed to react with 21 g. phosphorus pentoxide, 12.1 g. (0.05 mol) *o* - (*m* - methyl - phenoxymethyl) - benzoic acid are introduced at about 80°C. and the flask content heated for 30 minutes at 100—110°C., with intensive stirring. After working up as previously described, there are obtained 6.0 g. (54.0% of theory) 3 - methyl - dibenzo - (b,e) - oxepin - 11 - one of b.p. 139—147°C/0.1 mm Hg 1 m.p. 71—72°C (from ligroin/ether).

The *o* - (*m* - methyl - phenoxymethyl) - benzoic acid needed as starting material was obtained in the usual manner from ω - bromo - *o* - toluyl bromide and *m* - cresol in a yield of 77% of theory (m.p. 145—148°C.).

Example 10.

2 - methoxy - dibenzo - (b,e) - thiepin - 11 - one.

13.7 g. (0.05 mol) *o* - (*p* - methoxy - phenylmercapto) - benzoic acid are introduced at 100°C., with stirring, into 100 g. polyphosphoric acid and the mixture heated for 30 minutes at 100—110°C. After the usual working up, there are obtained 1.5 g. (12% of theory) 2 - methoxy - dibenzo - (b,e) - thiepin - 11 - one of b.p. 175—187°C/0.05 mm Hg and m.p. 89—90°C (from isopropanol).

The *o* - (*p* - methoxy - phenylmercaptomethyl) - benzoic acid required as starting material was obtained in the usual manner from ω - bromo - *o* - toluyl bromide and *p* - methoxy - thiophenol in a yield of 88% of theory (m.p. 116—119°C.).

Example 11.

General working method for the preparation of 11 - hydroxy - 11 - (3′ - aminopropyl) - dibenzo - (b,e) - oxepins or thiepins (III).

1.82 g. (0.075 gram atoms) magnesium turnings in 10 ml. absolute tetrahydrofuran and a few grains of iodine are first reacted with 0.5 ml. methyl iodide. A solution of 0.075 mol of an aminoalkyl halide in 10 ml. tetrahydrofuran is then allowed to drop

in, in such a manner that the solvent boils gently and the reaction mixture subsequently heated until all the magnesium has reacted, if necessary, with the renewed addition of aminoalkyl halide (about 10% excess). A solution of 0.05 mol of a dibenzo - (b,e) - oxepin- or thiepin - 11 - one (II) obtained as in Examples 1 to 10, in 10 ml. tetrahydrofuran, is then added dropwise at 20—30°C. and the flask content heated, with stirring, for 3 hours at 40—50°C. After the termination of the reaction, the reaction mixture is decomposed with about 30 ml. of a saturated ammonium chloride solution at about 15—20°C., water and ether added thereto and the organic portions separated off. After drying the combined ether extracts with anhydrous sodium sulphate and removing the solvent in a vacuum, there remains a residue which, after trituration with ligroin or ligroin-ether, yields the carbinols (III) in a sufficiently pure form for the further working up; the carbinols can, if necessary, be recrystallised from, for example, isopropanol.

In the following Table 1 are compiled the carbinols (III) produced according to this process:—

TABLE 1

Carbinols (III)	Yield (% of theory)	m.p. °C.
11-hydroxy-11-(3'-dimethylamino-propyl)-dibenzo-(b,e)-oxepin	86.5	118—119
11-hydroxy-11-(3'-piperidino-propyl)-dibenzo-(b,e)-oxepin	56.5	140—143
11-hydroxy-11-(3'-(N'-methyl-N-piperazinyl)-propyl)-dibenzo-(b,e)-oxepin	50.0	151—155
11-hydroxy-11-(3'-dimethylamino-propyl)-2-methyl-dibenzo-(b,e)-oxepin	72.3	123—127
11-hydroxy-11-(3'-dimethylamino-propyl)-2-methoxy-dibenzo-(b,e)-oxepin	73.5	107—111
11-hydroxy-11-(3'-dimethylamino-propyl)-2-chlorodibenzo-(b,e)-oxepin	82.7	140—144
11-hydroxy-11-(3'-dimethylamino-propyl)-2-methyl-dibenzo-(b,e)-thiepin	85.0	133—137
11-hydroxy-11-(3'-dimethylamino-propyl)-2-chlorodibenzo-(b,e)-thiepin	78.0	133—137
11-hydroxy-11-[3'-(N-benzyl-N-methyl)-aminopropyl]-dibenzo-(b,e)-oxepin	63.6	104—107
11-hydroxy-11-[3'-(N-benzyl-N-methyl)-aminopropyl]-dibenzo-(b,e)-thiepin	60.2	108—109

EXAMPLE 12.

General working method for the preparation of 11 - (3' - aminopropylidene) - dibenzo - (b,e) - oxepins or thiepins (I) from the carbinols (III):

I) 0.02 mol of an 11 - hydroxy - 11 - (3' - aminopropyl) - dibenzo - (b,e) - oxepin or -thiepin (III) obtained as in Example 11 are heated to boiling under reflux cooling for 1 hour in 25 ml. ethanolic hydrochloric acid (about 7—8N). After evaporation of the bulk of the ethanol in a vacuum and the addition of water and ether, the aqueous acidic portions are separated off, rendered alkaline with dilute sodium hydroxide solution and extracted with ether. The combined, washed and dried ether extracts are freed from solvent and the evaporation residue distilled in a high vacuum. The so obtained bases (I) are converted in the usual manner into their crystallisable salts.

In Table 2 are compiled the compounds (I) prepared according to this process.

2) In some cases, the production of the aminopropylidene compounds (I) can be carried out according to a simplified preparation variation;

0.02 mol 11 - hydroxy - 11 - (3' - dimethylaminopropyl) - dibenzo - (b,e) - oxepin obtained as in Example 1) are heated to boiling for 1 hour in 25 ml. ethanolic hydrochloric acid. The solvent is completely removed in a vacuum, the residue first treated several times with absolute ether and then brought to crystallisation with a mixture of isopropanol - ether. 11 - (3' - dimethylaminopropylidene) - dibenzo - (b,e) - oxepin hydrochloride of m.p. 184—186°C. (from methyl ethyl ketone) is obtained in a yield of 91% of theory.

TABLE 2.

alkylidene compounds (I)	Yield (% of theory)	b.p. (mm/°C.)	salts m.p. °C.
11-(3'-dimethylamino-propylidene)-dibenzo-(b,e)-oxepin	73.0	0.03/154—157	Maleate 161—164
11-(3'-piperidino-propylidene)-dibenzo-(b,e)-oxepin	85.0	0.2/190—195	Succinate 136—138
11-(3'-(N'-methyl-N-piperazinyl)-propylidene)-dibenzo-(b,e)-oxepin	55.0	0.1/200—205	HCl-Salt $1/2H_2O$ 256—258 (decomp.)
11-(3'-dimethylamino-propylidene)-2-methyl-dibenzo-(b,e)-oxepin	65.0	0.3/164—167	HCl-Salt 176—178
11-(3'-dimethylamino-propylidene)-2-methoxy-dibenzo-(b,e)-oxepin	68.0	0.3/183—185	HCl-Salt $1/4H_2O$ 183—185
11-(3'-dimethylamino-propylidene)-2-chlorodibenzo-(b,e)-oxepin	79.7	0.3/176—181	HCl-Salt 216—182
11-(3'-dimethylamino-propylidene)-2-methyl-dibenzo-(b,e)-thiepin	82.2	0.15/176—180	HCl-Salt 206—208
11-(3'-dimethylamino-propylidene)-2-chlorodibenzo-(b,e)-thiepin	73.7	0.1/178—185	HCl-Salt $1/4H_2O$ 234—236
11-[3'-(N-benzyl-N-methyl)-aminopropylidene]-dibenzo-(b,e)-oxepin	92.6	0.1/220—230	—
11-[3'-(N-benzyl-N-methyl)-aminopropylidene]-dibenzo-(b,e)-thiepin	87.6	0.15/210—225	—

EXAMPLE 13.

General working method for the production of 11 - (3' - aminopropylidene) - dibenzo - (b,e) - oxepins and thiepins by the "one pot process".

As described above, 1.82 g. magnesium, 0.075 mol aminoalkyl halide and 0.05 mol of a dibenzo - (b,e) - oxepin- or -thiepin - 11 - one (II) obtained as in Examples 1 to 10 are allowed to react in a total of 30 ml. tetrahydrofuran, 40—50 ml. dilute hydrochloric acid added thereto and the flask content brought to boiling for 2 hours, with stirring. After the addition of ether and water, the aqueous acid portions are separated off, rendered alkaline with concentrated ammonia and the basic portions which separate out taken up in ether. The combined, washed and dried ether extracts are freed from solvent and the evaporation residue distilled in a high vacuum, whereupon the

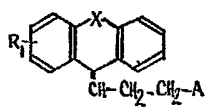
so obtained bases (I) can, if desired, be converted in the usual manner into their crystallisable salts.

In the following Table 3 are compiled the compounds (I) obtained by this process.

Alkylidene compound (I)	Yield (% of theory)	b.p. (mm/°C.)	salts m.p. (°C.)
11-(3'-dimethylamino-propylidene)-dibenzo-(b,e)-oxepin	86.8	0.08/164/170	Maleate 161—164
11-(3'-dimethylamino-propylidene)-2-chlorodibenzo-(b,e)-thiepin	70	0.1/178—185	HCl-Salt $1/4H_2O$ 234—236
11-[3'-(N'-methyl-N-piperazinyl)-propylidene]-dibenzo-(b,e)-thiepin	38.5	0.07/210—215	HCl-Salt 255—257

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



wherein X is an oxygen or sulphur atom, R_1 is a hydrogen or halogen atom or an alkyl or alkoxy radical and A is a tertiary amino group with the proviso that where x is a sulphur atom and R_1 is a hydrogen atom, A is other than a dimethylamino group; and the acid addition salts and quaternary ammonium compounds thereof.

2. Compounds according to claim 1, wherein the tertiary amino group A is a dialkylamino group or an unsubstituted or substituted nitrogen-containing heterocyclic radical.

3. 11 - (3' - dimethylamino - propylidene) - dibenzo - (b,e) - oxepin.

4. 11 - (3' - piperidino - propylidene) - dibenzo - (b,e) - oxepin.

5. 11 - (3' - (N' - methyl - N - piperazinyl) - propylidene) - dibenzo - (b,e) - oxepin.

6. 11 - (3' - dimethylamino - propylidene) - 2 - methyl - dibenzo - (b,e) - oxepin.

7. 11 - (3' - dimethylamino - propylidene) - 2 - methoxy - dibenzo - (b,e) - oxepin.

8. 11 - (3' - dimethylamino - propylidene) - 2 - chlorodibenzo - (b,e) - oxepin.

9. 11 - (3' - dimethylamino - propylidene) - 2 - methyl - dibenzo - (b,e) - thiepin.

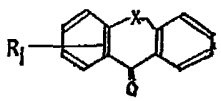
10. 11 - (3' - dimethylamino - propylidene) - 2 - chlorodibenzo - (b,e) - thiepin.

11. 11 - (3' - (N - benzyl - N - methyl) - aminopropylidene) - dibenzo - (b,e) - oxepin.

12. 11 - (3' - (N - benzyl - N - methyl) - aminopropylidene) - dibenzo - (b,e) - thiepin.

13. 11 - (3' - (N' - methyl - N - piperazinyl) - propylidene) - dibenzo - (b,e) - thiepin.

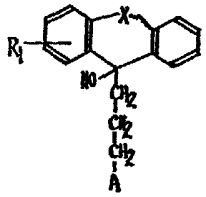
14. Process for the production of compounds of the general formula given in claim 1, wherein a cyclic ketone of the general formula:—



in which R_1 and X have the same meaning as above, is reacted with a Grignard compound of the general formula:—

$$Hal—Mg—CH_2—CH_2—CH_2—A$$

in which A has the same meaning as above and Hal is a halogen atom, and the addition product so obtained decomposed to give a carbinol of the general formula:—



in which A, R_1 and X have the same meaning as above, and water then split off from this carbinol to give the desired compound.

15. Process according to claim 14, wherein the Grignard compound is added to 20—30°C. and the reaction mixture subsequently heated at 40—50°C.

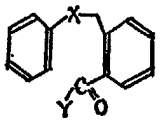
16. Process according to claim 14 or 15, wherein the Grignard addition product is

decomposed to the carbinol with an ammonium chloride solution.

17. Process according to any of claim 14 to 16, wherein the carbinol is converted into the desired end product by the action of alcoholic hydrochloric acid.

18. Modification of the process of claim 14, wherein the Grignard addition product is boiled with hydrochloric acid to give directly the desired end product.

19. Process according to any of claims 14 to 18, wherein the cyclic ketone used as starting material is obtained by the internal condensation of a benzoic acid derivative of the general formula:—



in which X has the same meaning as above and Y is a halogen atom or a hydroxyl group.

20. Process according to claim 19 in which Y is a hydroxyl group, wherein the internal condensation is brought about by the use of a phosphoric acid ester or polyphosphoric acid.

21. Process according to claim 19 in which Y is a halogen atom wherein the internal condensation is brought about by the use of aluminum chloride.

22. Process according to claim 19, in which Y is a halogen atom, wherein the internal condensation is brought about by heating the acid halide in the presence or absence of a solvent.

23. Process for the production of compounds of the general formula given in claim 1, substantially as hereinbefore described.

24. Process for the production of compounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

25. Compounds according to claim 1, whenever prepared by the process according to any of claims 14 to 24.

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Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to Patents Nos. 1,001,822, 1,001,823, 1,001,824 and 1,001,825.

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